**I Antibiotics**

Key concepts: Synergism, antagonism, zone of inhibition, MIC, MBC, Tube/Plate dilutions, Multidrug therapy, bacterial resistance, cross hypersensitive

Targets of antibiotics include: Cell wall synth, Protein synthesis, Nucleic acid synthesis, Metabolite synthesis and Cell membrane disruption.

Ex: Fluroquinolones inhibit supercoiling of circular DNA, Rifampin impairs prokaryote RNA Pol

Ex: Polymyxin B- used in gram (-) cells to disrupt the membrane causing leakage (also impacts Euk so no longer used)

Ex: sulfa drugs bind to metabolite enzymes and inhibit by competitive inhibition

**II Cell wall inhibitors**

Types: Beta lactams (Penicillin, Cephalosporins, carbapenems, monobactams) Other (Vancomycin, bacitracin, Daptomycin)

🚑 Penicillin:

1. Natural penicillins: Common strep infections, URTI, Pneumonia meningitis, prophylaxis of RH
   1. Pen G: targets g+ coccus *staph aureus, strep pyogens, s. influenza, s. viridians*/ g- coccus *neisseria gonorrhea, n. meningitidis*/ g- bacilli *bacteroides* (escept *fragile)*/ other (Treponema pallidum and chlamidia). Can be used with **probenicid** (decrease renal secretion) or conjugated with **procaine** or **benzathine** as repository penicillin. Procaine (12-24 hr IM but rarely used because of increases in penicillinase *gonorrhea)* Benzathine (3-4 weeks IM used for Rhematic Fever, Syphilus, *strep pharyngitis.)* Pen G is not acid tolerant and has 7 adverse **side RX**
      1. **Serum sickeness/rash 1/10000**
      2. **Neurotoxicity- coma and seizures**
      3. **Cation toxicity- give as a salt with Na or K**
      4. **Fluid/ph imbalance- Na is swapped for K and H so hypocalemic and alkalosis**
      5. **Herxheimer Rx- flu symptoms, rash at syphilitic lesions; resolution in 2 weeks**
      6. **Coombs (+) hemolytic anemia- anemia in 10%**
      7. **Interstitial nephritis (reason methcillin was revoked)**
   2. Pen V: similar to G but acid resistant due to a phenoxymethyl instead of a benzyl R group. Still has a similar spectrum as Pen G.
2. B-Lactamase Resistant Penicillins: Used exclusively for penicillin resistant *S. aureus*  (less active than other forms of penicillin against other micro organisms)
   1. Methicillin: no longer used because of Interstitial nephritis
   2. Oxacillin, Cloxacillin, Dicloxacillin: used for *staph areus*
   3. Nafcillin: eliminated by biliary excretion so no kidney issues and decreased likelihood of CNS toxicity do to impaired renal function. Prescribed in cases of epidemic *staph*, bacterimia
3. Broad spectrum Antibiotics (amino, carboxy, ureido- penicillins) all sensitive to Betalactamases
   1. Amoxicillin- aminopenicillin against *E. coli, Proteus mirabilis,* salmonellae and haemophilius species; better absorbed orally and lower GI disturbance. Works with B-Lase inhibitor **Clavulanate.\*\* Possible RX includes Diarrhae.**
   2. Ampicillin- aminopenicillin “ : both oral and parenteral use with increased activity against *shigella and listeria.*  Works with B-Lase inhibitor **Sulbactam. \*\*Possible SideRX includes Diarrhea.**
   3. Indanyl Carbenicillin: carboxypenicillin with extended spectrum to include *Pseudomonas, Proteus (*indole positive); High concentrations in the urine makes this good for UTI. **\*\* Possible RX includes bleeding (inhibits clotting).**
   4. Ticarcillin: Carboxypenicillin “ ; works with B-Lase inhibitor **Clavulanate.** **\*\* Possible SideRX includes bleeding (inhibits clotting).**
   5. Piperacillin: Ureidopenicillins with a similar spectrum as ticarcillin but also includes *Klebsiella pneumonia*. NOT acid stable. Works with B-Lase inhibitor **Tazobactam**
   6. Mezlocillin: Ureidopenicillins “ .

NOTE: Beta Lactamases are often produced by Penicillin resistant microbes. The subtypes of B-Lases include – Serine penicillinase, metallo-B-lactamase, Cephalosporinase, oxacillinase, carbapenemases, Extended spectrum B-Lases (ESBLs)

🚑 Cephalosporins

1. Class 1: effective against many g(-) and g(+); Resistant to *S. areus* B-Lase; broader spectrum than Pen G and useful against *K. pneumonia and E. coli.*
   1. Cefazolin: parenteral, cleared by kidneys, plasma life 2hrs.
   2. Cephalexin: oral, no signs yet of kidney damage as a side effect
2. Class 2: effective against many g(-) and g(+); better than class 1 at targeting *Haemophilus*
   1. Class B Cefotetan: parenteral, better at anaerobes like *B. fragile (*Note that Pen G couldn’t do this class)
   2. Class B Cefoxitin: also active against *B.fragile*
   3. Class A Cefuroxime: oral, only drug of the 2nd class to reach CNS at therapeutic levels, enhanced activity against B-Lase producing *H.influenzae, M.catarrhalis* respiratory infections.
   4. Class A Cefamandol: excellent against *H.influenzae*
   5. Class A Cefonicid: excellent against *H.influenzae*
   6. Cefprozil: oral, better at penicillin-sensitive *Strep, E.coli, Proteus, Klebsiella, and Citrobacter.*
3. Class 3: extended spectrum to include *Pseudomonas, Enterobacter, Serratia, Proteus.* Made stable against many B-Lases by **oxime ether group** on the R. **Aminothiazole ring** improves the attatchment and entry into the periplasm.
   1. Ceftriaxone: parenteral; used for *Gonorrhea*. Some other g(-) but long plasma life at t1/2 being 8hrs. Cleared by biliary system
   2. Cetazidime: parenteral; used for *Psuedomonas* (also with aminoglycosides for *psuedomonal* meningitis)
   3. Cefdinir: oral drug to for B-Lase respiratory infections
4. Class 4: stable to hydrolysis by B-Lase plasmids and a poor inducer of chromosomal B-Lase and mostly resistant to their activity. Not stable to ESBLs.
   1. Cefepime: no details

🚑 Carbapenems: good for emergency treatment and no cross resistance with B-lases

1. Imipenem-cilastatin: the **cilastatin** inhibits the renal enzyme that inactivates the imipenem and also prevents renal toxicity by inhibiting active uptake of the drug into the renal tubules. **Possible sideRX includes CNS toxicity since the cilastatin prevents the drug from being transported out of CSF**
2. Meropenem: broad spectrum like imipenem with less activity to g(+) and more activity to g(-). It is not hydrolyzed by the same kidney enzyme so you do not need cilastatin which also decreases the risk of CNS toxicity

🚑 Monobactams: small class that has little cross hypersensitivity

1. Aztreonam: binds to PBP-3 which is only on aerobic g(-) bacteria. Resitant to most B-Lases, doesn’t induce the chromosomal B-lases, can be inhibited by chromosomal B-Lases (ESBL) already activated by other means. Little risk of cross-hyerpsensitivity with penicillins or cephalosporins.

🚑 Other: these can be cell wall inhibitors or a few a few protein synth inhibitors that are used in the place of B-lactams

1. Spectinomycin: (Protein synth inhibition) 1 IM inj for urethral *gonorrhea*; useful if allergic to penicillins and has low toxicity. **Side RX: nausea, chills, fever, dizziness**
2. Vancomycin: (cell wall inhibition) blocks the two terminal D-alanines preventing the transpeptidase from making cross-links in the cell wall. Many **Side RX:**
   1. **Ototoxic- occasionally irreversible**
   2. **Nephrotoxic- blood in urine**
   3. **Thomobophlebitis- clots in bloodstream occur over 10% of patients**
   4. **Hypertension- drug releases histamine**
3. Quinupristin/dalfopristin: (two protein inbhibitors) used against vancomycin/multidrug resitant *enterococcus faecium.*  HAS NO EFFECT ON *enterococcus faecalis.* **Side RX: muscle and joint pain**
4. Linezolid: (protein inhibitors) parenteral and oral for vancomycin resistant *enterococcus.* Binds part of the large ribosomal subunit with little cross resistance occurring between it and other protein inhibitors. **Side RX include thrombocytopenia if over two weeks of meds. Blocks the MAO so shouldn’t eat tyramine rich foods b/c will increase BP.**
5. Daptomycin: Cyclic lipopeptide that inserts in the membrane, binds other units and creates porins that create a leaky membrane. Used in skin infections especially  *MRSA, S.pyogens, S.aglactiae, S.dysgalatiae, E.faecalis(vanco sensitive)*. NOT EFFECTIVE AGAINST RESP INFECTIONS. **Side RX: rabdomyolysis and paresthesias**

**III Protein Synthesis Inhibition (see above for a few that we have already discussed)**

🚑 Macrolides: 50s ribosomal unit that causes inhibition of peptidyl-tRNA translocation;

1. Erythromycin: resp/urinary infections for *S.pneumonia, S.pyogens, Chlamydia trachomatis, Mycoplasma pneumonia, Legionella.* Drug ester is more stable in ester form (estolate). **Side RX:** 
   1. **Cholestatic hepatitis: less than 1%, older than 12, sx after 2weeks with severe abdominal pain, fever and itchy skin. Reversible after stop meds**
   2. **Arrhythmias**
   3. **Temp hearing loss: >4g perday**
   4. **Gastrointestinal cramps: 50% due to its activation of MMC (mitigate with glycopyrrolate)**
2. Clarithromycin and Azithromycin: substitues for erythromycin with less side effects, same spectrum, treat mycobacterial pneumonia with Zpack having less effect on P450 and better for Chlamydial

🚑 Clyndamycin: 50s unit, used in prophylaxis for dentals and severe infections outside the CNS like *B.fragiles (*remember that PenG couldn’t handle but Class II cephalosporins could). Used, in combination with aminoglycosides, too treat penetrating wounds of abdomen and aspiration pneumonia. **Side RX include diarrhea in 10%, skin rashes (rarely Steven-Johnsons synd) hepatotoxicity**

1. Metronidazole: only for anaerobes; well absorbed orally and well distributed. Great for c*lostridum difficile, B.fragilis, protozoa Trichomonas vaginalis and Giardia*. S**ide RX include GI problems but can also show parasthesia, disulfiram rx (if drink alcohol), ataxia/convulsions and maybe carcinogenic**

🚑 Tetracyclines: 30s unit to inhibit tRNA binding; \*\*Bacteriostatic\*\* broad spectrum for +/-; drug of choice for: rickettsial inf, cholera, chlamydia, acne (classic structure is 4 carbon rings with side groups). **Side RX**

* 1. **Hepatotoxicity: greater than 1-2 grams per day with jaundice and usually fatal (especially in pregnancy)**
  2. **Neprotoxicity: patients with renal disease might tolerate Doxycycline but others cause toxicity. May cause Fanconi syndrome in healthy patients**
  3. **Deposition in children under the age of 8 (yellow teeth)**
  4. **Gastro irritation if taken orally**
  5. **Phototoxicity**
  6. **Minocylcine can cause vertigo, ataxia, nausea due to damage to the middle ear but this is reversible**
  7. **Can impair calcium, magnmesium, aluminum absorption**
  8. **Interferes with clotting since it can impair anticoagulant drugs**
  9. **DO NOT TAKE IF pregnant, child or renal impairment**

**NOTE: Tigecycline is a derivative of minocycline and only ever given IV. Great for bacteria resistant to other tetracyclines. Has a broad spectrum against *Methicillin/Vancomycine Resistant S.aureus* and ESBLs**

🚑 Choramphenicol: 50s unit to prevent binding of the amino acid part of aminoacyl-tRNA. Back up drug to B-lactams for *H.infulenza, N.meningitidis,* and also a back up for tetracyclines where you cannt give to children/pregnant/renalfailure. **Side RX: decrease in bone marrow can cause anemia, optic neuritis leading to blindness, diarrhea, gray baby syndrome from being hypoxic due to HBP**

🚑 Aminoglycoside: 30s unit and cause misreading of the genetic code. \*\*Bacteriocidal\*\* used against aerobic g(-) rods and some g(+). Paterenteral for systemic infections, cleared by kidney, can be inactivated by Nacetylation, Ophosphorylation, Oadenylation. Method of action is energy dependent and requires oxygen. **Side RX are Nephrotoxcicity with increased BUN after a week or two. Loop diuretics can potentiate renal toxicity. Sometimes permanent ototoxicity (accumates in perilymph), vestibular damage and cochlear damage.**

1. Streptomycin: pulmonary TB
2. Gentamycin: 1st choice drug because of its cost and spectrum. Hits *Psuedomonas*
3. Tobramycin: somewhat enhanced activity against *Psuedomonas*
4. Amikacin: used when genta/tobramycin resistant organisms. Can only be inactivated at 6’
5. Netilmicin: used for genta/tobramycin resistant organisms

NOTE: AG have poor therapeutic index but they have a post antibiotic effect which means you can slow the microbial growth even after blood levesl fall below the MIC. This allow once daily dosing hoping to peak at 5-10 units in the plasma but then falling below the 2 unit mark between doses (2+ causes toxicity if maintained for a few days). Neuromuscular junction blockades have been seen with overdosing. Also hypersensitivity (rash, fever, chills…) and suprainfections can also result.

**IV Nucleic Acid Inhibitors**

🚑 Quinolones/Fluoroquinolones: bacteriocidal drugs that inhibit the supercoiling and uncoiling of circular DNA in Prokaryotes. Drugs target Topoisomerase II and IV. Fluoroquinolones have the added advantage of passing across host membranes to target intracellular microbes.NOTE: Mostly used to treat UTI, Diarrhea (*Ecoli, salmonella, shigella, campylobacter*…), *gonoccocal*, respiratory infections, prophylaxis for anthrax. Resistance develops rapidly to these drugs… resistant to 1 = resistant to all.

1. Nalidixic acid: quinolone 1st generation; used for UTI *E.coli, Klebsiella, Enterobacter, Proteus.*
2. Ciprofloxacin: fluoroquinolone 2nd gen: broad spectrum. Most effective against a wide array of bacteria. Potent CP450 inhibitor and increases the toxic effects of anticoagulants, digoxin, theophylline. Long post-antibiotic effect, administered orally, excreted in the urine
3. Levifloxacin: fluoroquinolone 3rd gen: broad spectrum but most effective against respiratory infections
4. Moxifloxacin: fluoroquinolone 4th gen: broad spectrum but most effective against respiratory infections and also active against anaerobic infections

**Side RX:**

* **Both Q and FQ- bone/cartilage abnormalities, tendonitis/tendon tear, CNS toxicity, Cardiac effects, phototoxicity**
* **Only FQ- Hepatotoxicity, hypoglycemic in elderly diabetics, hyperglycemic in non-diabetics, rashes (0.5-2.0% of cases)**
* **Drug interactions: antacids reduce oral bioavailability; FQ increase warfarin’s efficacy and theophylline’s plasma concentration**

🚑 Rifampin: broad spectrum of action but mostly used against tuberculosis since resitance development is common. Drug targets prokaryotic DNA dependent RNA pol. Widely distributed (including the CNS). Common **side RX: hepatotoxicity, hypersensitivity, orange body fluids, increased cytochrome p450.** (Derivatives include Rifabutin and Rifapentine)

**V Antimetabolites**

🚑 Sulphonamide drugs: competitive inhibition of enzyme active site. It is mainly used in drug combination therapy with dihydrofolate reductase inhibitors (trimethoprim) for susceptible organisms, specifically in the urinary tract. However, the relatively large number of side effects have made this a not so popular treatment choice given all the other possible antibiotics to choose from. Although its antibacterial merit is of lesser value, its use as a diuretic, cox-2 inhibitor and its treatement applicability in inflammatory bowel disease are all current uses for the drug.